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COMMUNICATION

Consecutive iridium catalyzed C–C and C–H bond forming hydrogenations for the diastereo- and enantioselective synthesis of *syn*-3-fluoro-1-alcohols: C–H (2-fluoro)allylation of primary alcohols†

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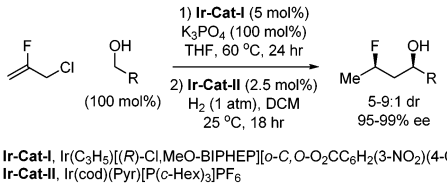
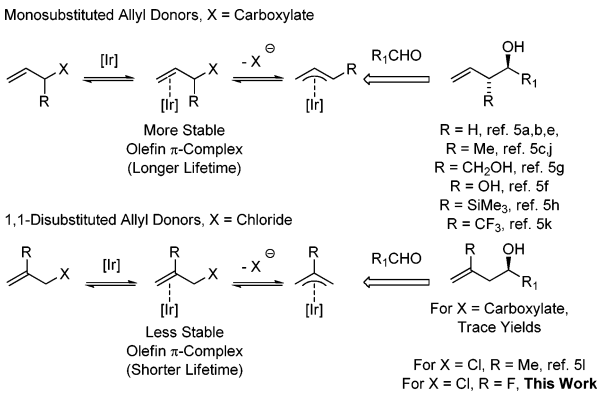
Commercially available (2-fluoro)allyl chloride serves as an efficient allyl donor in highly enantioselective iridium catalyzed carbonyl (2-fluoro)allylations from the alcohol or aldehyde oxidation level *via* transfer hydrogenation. Diastereoselective Crabtree hydrogenation of the resulting homoallylic alcohols provides *syn*-3-fluoro-1-alcohols.

Organofluorine compounds represent over 20% of approved pharmaceutical agents and 30–40% of commercially available agrochemicals.[1] The importance of organofluorine compounds, along with the fact that approximately 80% of the small molecule drugs entering the market are estimated to contain one or more chiral centers,[2] have driven development of enantioselective methods for the preparation of fluorinated compounds.[3] Under the conditions of C–C bond forming transfer hydrogenation,[4,5] we recently reported an enantioselective iridium catalyzed carbonyl (α-trifluoromethyl)allylation from the alcohol or aldehyde oxidation level.[5k] Given the commercial availability of (2-fluoro)allyl chloride, corresponding carbonyl (2-fluoro)-allylations were considered. Remarkably, despite decades of work on enantioselective carbonyl allylation,[6] enantioselective carbonyl (2-fluoro)allylations have not been reported. Here, under the conditions of iridium catalyzed transfer hydrogenation, we report the first enantioselective (2-fluoro)allylations, which are achieved with equal facility from the alcohol or aldehyde oxidation level. These adducts participate in diastereoselective Crabtree hydrogenation,[7] enabling the synthesis of *syn*-3-fluoro-1-alcohols *via* consecutive C–C and C–H bond forming hydrogenations (Scheme 1).

Olefin coordination is a prerequisite to the ionization of allylic leaving groups by low valent transition metals. Consequently, in iridium catalyzed carbonyl allylations employing allylic carboxylates, allyl donors that incorporate monosubstituted olefins are generally required, as the stability of late transition metal-olefin π-complex decreases with increasing degree of olefin substitution.[8] In recently established catalytic C–C couplings of methallyl chloride,[5l] it was found that use of a more reactive leaving group in the form of chloride compensates for the shorter lifetime associated with more highly substituted olefin-iridium complexes. To probe the expansion of substrate scope potentially availed by this effect, and given the aforementioned significance of organofluorine compounds, a study on the use of (2-fluoro)allyl chloride as an allyl donor was undertaken (Scheme 2).



Scheme 1 Synthesis of *syn*-3-fluoro-1-alcohols *via* consecutive C–C and C–H bond forming hydrogenations.



Scheme 2 More reactive chloride leaving groups compensate for decreased stability of π-complex.

Studies began with a preliminary screen of (2-fluoro)allyl chloride and alcohol **2g** using the chromatographically isolated cyclometallated iridium π-allyl complex of 4-cyano-3-nitrobenzoic acid and BIPHEP under conditions optimized for the reaction of methallyl chloride.[5l] Although the product **4g** was obtained in good isolated yield, competing defluorination to form **5g** was observed. Attempts were made to attenuate this side reaction. Variation of solvent, concentration and base provided no improvement beyond the initially applied conditions, which involve THF (1.0 M) and K_3PO_4 (100 mol%). Reaction temperature had a more

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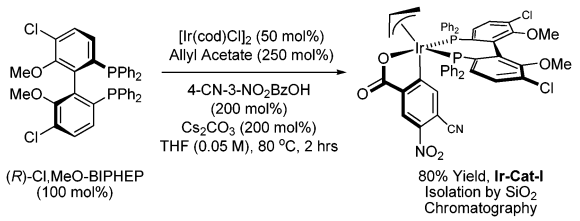
† Electronic supplementary information (ESI) available: Characterization data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS, [α]). Absolute stereochemical assignment of **6g** by single crystal X-ray diffraction. CCDC 867899. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc31743e



Scheme 3 Preparation of iridium complex **Ir-Cat-I**.

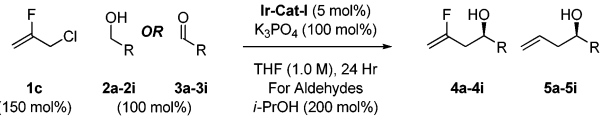
significant impact. For allylic and benzylic alcohols, which dehydrogenate and, hence, couple at lower temperature, reactions conducted at 40 °C were optimal in terms of maximizing product formation and minimizing defluorination. For aliphatic alcohols, the optimal reaction temperature was determined to be 60 °C.

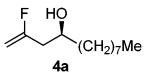
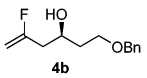
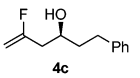
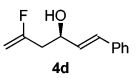
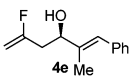
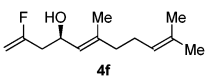
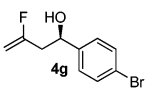
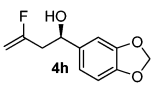
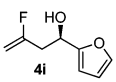
To assess whether these trends in reactivity translate to enantioselective processes, the chiral complex **Ir-Cat-I** (Scheme 3), which is isolated by conventional silica gel chromatography, was prepared and assayed in the coupling of (2-fluoro)allyl chloride to alcohols **2a–2i**. To our delight, aliphatic alcohols **2a–2c**, allylic alcohols **2d–2f** and benzylic alcohols **2g–2i** participate in highly enantioselective C–C coupling to furnish the corresponding products of (2-fluoro)allylation **4a–4i**. In general, the products of (2-fluoro)allylation **4a–4i** may be separated from the defluorination products **5a–5i** by silica gel chromatography. However, to ensure an accurate evaluation of the product distribution, **4a–4i** and **5a–5i** were isolated as mixtures (Table 1). An equivalent set of adducts **4a–4i** may be generated from aldehydes **3a–3i** using isopropanol as the terminal reductant under otherwise identical conditions. Comparable isolated yields and enantioselectivities are observed. Thus, carbonyl (2-fluoro)allylation may be accomplished from the alcohol or aldehyde oxidation level (Table 1).

With adducts **4a–4i** in hand, methods for diastereoselective hydrogenation were explored. Reduction of **4g** occurs efficiently using palladium on carbon, however, the saturated product **6g** forms as a 1 : 1 mixture of diastereomers. In contrast, using the Crabtree catalyst,[7] hydrogenation of **4g** at 25 °C provides **6g** as a 6 : 1 mixture of diastereomers favouring the *syn*-diastereomer. Under these conditions, vinyl fluorides **4a–c** and **4g** were converted to the *syn*-3-fluoro-1-alcohols **6a–c** and **6g**, respectively (Scheme 4). In these experiments, it was found that diastereoselectivity improved with lower temperature, lower loadings of the Crabtree catalyst and higher dilution. Fortuitously, the *syn*-3-fluoro-1-alcohol **6g** is crystalline, allowing relative and absolute stereochemical assignment *via* single crystal X-ray diffraction analysis† by the anomalous dispersion method. On this basis, the absolute stereochemistry of (2-fluoro)allylation products **4a–4i** is assigned.

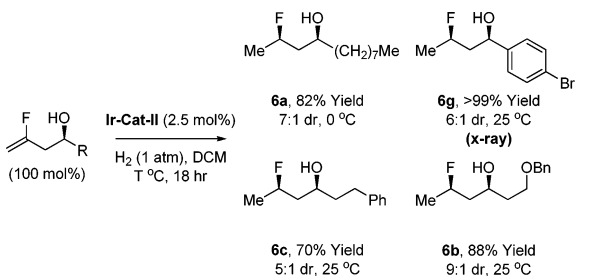
In summary, using commercially available (2-fluoro)allyl chloride, direct enantioselective iridium catalyzed C–H (2-fluoro)-allylation of primary alcohols **2a–2i** is achieved. Corresponding aldehydes **3a–3i** participate in carbonyl (2-fluoro)allylation to furnish an identical set of adducts **4a–4i** in the presence of isopropanol under otherwise identical conditions. Diastereoselective Crabtree hydrogenation of the resulting vinyl fluoride containing homoallylic alcohols **4a–c** and **4g** provides *syn*-3-fluoro-1-alcohols **6a–c** and **6g**, respectively. Thus, using consecutive C–C and C–H bond forming hydrogenations, primary alcohols are converted to chiral fluorine containing building blocks in the

Table 1 Enantioselective iridium catalyzed (2-fluoro)allylation from the alcohol or aldehyde oxidation level[a]



Entry	Product	[o] Level	Y [%] **4a** (**5a**)	ee [%]
1	 **4a**	Alcohol	76 (10)	99[b]
		Aldehyde	61 (5)	99[b]
2	 **4b**	Alcohol	65 (6)	98[b]
		Aldehyde	55 (6)	98[b]
3	 **4c**	Alcohol	89 (5)	99[b]
		Aldehyde	65 (6)	98[b]
4	 **4d**	Alcohol	76 (4)	98[c]
		Aldehyde	74 (3)	98[c]
5	 **4e**	Alcohol	80 (5)	98[c]
		Aldehyde	93 (4)	98[c]
6	 **4f**	Alcohol	75 (4)	95[c]
		Aldehyde	74 (3)	96[c]
7	 **4g**	Alcohol	86 (7)	99[c]
		Aldehyde	89 (5)	99[c]
8	 **4h**	Alcohol	81 (3)	99[c]
		Aldehyde	88 (5)	99[c]
9	 **4i**	Alcohol	65 (5)	99[c]
		Aldehyde	73 (5)	99[c]

[a] Products **4** and **5** are isolated as mixtures, but were separated for the purpose of characterization. See Supporting Information for further details. [b] 60 °C. [c] 40 °C.



Scheme 4 Synthesis of *syn*-3-fluoro-1-alcohols **6a–c** and **6g** *via* Crabtree hydrogenation of vinyl fluorides **4a–c** and **4g**, respectively.

absence of stoichiometric metallic reagents or stoichiometric organic byproducts.

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